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Applicants:	Masahiko KOIKE et al.
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DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam/Sir:

I, Masahiko Koike, the undersigned, a citizen of Japan residing at 2-2-29, Senrien, Toyonaka-shi, Osaka 560-0046, JAPAN, do hereby declare:

I graduated from Toyama Medical and Pharmaceutical University with a degree of Master of Science in March 1991, and I was a visiting scientist in the Department of Industrial and Physical Pharmacy at Purdue University from April, 2005 to March, 2006.

I have been employed by Takeda Pharmaceutical Company Limited, Osaka, Japan, the Assignee of the present application, and have been engaged in pharmaceutical research therein since April, 1991. I am not receiving any additional compensation for preparing this Declaration other than my normal compensation as an employee at Takeda Pharmaceutical Company Limited.

I am one of the co-inventors of the present patent application. I have reviewed and am familiar with the February 03, 2009 Office Action and the references cited therein. In my opinion, the presently claimed invention is patentable over the prior art, particularly in view of the unexpected desirable properties provided thereby as described below. The experimental results described below were obtained by myself or under my supervision.

Challenges encountered in the prior art

The most common form of a drug containing two active ingredients (a "combination drug") is in the form of a bilayer laminate tablet having two layers, each layer independently containing one of the two active ingredients to achieve bioequivalence. However, a laminate tablet in the case of containing a high dosage has a drawback of being so large that the ingestion thereof can be difficult, thereby resulting in patient discomfort.

The biological equivalence of an active ingredient in the field of pharmaceutical preparations is generally examined *in vitro* by a fixed dose combination (FDC) dissolution test, during which the dissolution profile, including the dissolution rate, of an ingredient in a test vessel is observed. The Paddle method is a representative dissolution test method as defined in the *U.S. Pharmacopoeia* and is described in the present Specification (e.g., Experimental Example 3). According to the Paddle method, a solid preparation is dissolved in a test solution (900 mL, buffer (pH 2.0)) and its dissolution profile is observed. If the result of a dissolution test of an active ingredient in a combination drug and that of the same active ingredient in another drug containing the active ingredient as the only active ingredient show similar dissolution profiles, the active ingredients in the two drugs are considered to have a similar effect upon the blood concentration profiles in the subject. Additionally, the active ingredients in the two drugs are deemed to be "bioequivalent."

Pioglitazone hydrochloride exhibits a solubility of about 0.4 mg/mL in an acidic solution with a pH in the range of 2.0, which is the pH of the buffer used in the Paddle method. In one dissolution test by the Paddle method (test solution pH 2.0) with pioglitazone (pioglitazone

hydrochloride, or Actos®, Takeda, Osaka, Japan) being the single active ingredient in a drug preparation, the dissolution profile shows a dissolution rate of not less than 70% (98.9%) in 30 min and almost 100% in 1 hr. Additionally, as shown in Experimental Example 3 in the present application, when a combination drug containing pioglitazone (pioglitazone hydrochloride) having a median size of 1 to 25 μm and metformin (metformin hydrochloride, or Glucophage®, Bristol-Myers Squibb Co., Princeton, U.S.) having a median size of 10 to 100 μm was tested (preparations of Examples 2, 3, 5, and 6 with a median size ratio of about 2.2 or 8.1), the results of a dissolution test by the Paddle method revealed a similar dissolution profile, including a dissolution rate of not less than 70% in 30 min and almost 100% in 1 hr (*See* Table 3, present application). Thus, the pioglitazone in the combination drug of the present invention and that in a drug with a single active ingredient (Actos®) were shown to be equivalent *in vitro*.

However, it was found in one experiment that when a combination drug, which contained pioglitazone (pioglitazone hydrochloride) and metformin (metformin hydrochloride) as active ingredients and the median size of the pioglitazone was about 13 μm, was administered to a human and the blood concentration profiles of these active ingredients were examined during *in vivo* clinical studies, the pioglitazone (pioglitazone hydrochloride) in the combination drug was not found to be bioequivalent to that in a drug with pioglitazone as the single active ingredient. By contrast, during clinical studies, metformin (metformin hydrochloride) in the combination drug was found to be bioequivalent to that in a drug with metformin as the single active ingredient. The results described above are summarized in Table D1 below.

Table D1. Bioequvalence results of the two ingredients – pioglitazone and metformin as observed during *in vitro* dissolution test and clinical results.

Fixed Dose Combination (FDC)	*In vitro* Dissolution	Clinical Results
pioglitazone	Equivalent to Actos®	Not bioequivalent to Actos®
metformin	Not equivalent to Glucophage®	Bioequivalent to Glucophage®

Unexpected success provided by present invention

The discrepancies between the *in vitro* dissolution test and the clinical studies were likely a result of the complex interactions between the two active ingredients (pioglitazone and metformin) *in vivo*, which is a rare and unpredictable occurrence. However, these discrepancies can be eliminated, thereby achieving bioequivalence for both pioglitazone and metformin, when the median particle size of pioglitazone in the present combination drug was reduced to between 2 and 10 μm ("micronized"). Moreover, it was observed that micronization of the pioglitazone had no significant effect upon the uniformity of both of the active pharmaceutical ingredients.

In sum, a median size of pioglitazone at 2-10 μm has enabled control of the blood concentration profile of a combination drug to fall within a desired range, thereby achieving bioequivalence for both the pioglitazone and metformin in the presently claimed combination drug. At the same time, reducing the particle size of pioglitazone to this range did not significantly affect the uniformity of either of the active pharmaceutical ingredients.

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I declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 24th day of July, 2009.

Masahiko Koike

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